

REVENUDICATIONS

1. Sustained release microgranules containing a Ginkgo Biloba extract, characterized by the release of total flavone glycosides having the following profile of dissolution rates measured at $37.0^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$, with a Dissolution Test Apparatus I (Basket method at 100 rpm, 900 mL of purified water UV Detection : 272 nm) :

T (h)	DISSOLUTION (w/w)
0,5 hour	$\leq 45 \%$
2 hours	$< 75 \%$
8 hours	$> 60 \%$

2. Sustained release microgranules according to claim 1, characterized by the following profile :

T (h)	Dissolution (w/w)
0,5 hour	5-45 %
2 hours	30-70 %
8 hours	$> 60 \%$

3. Sustained release microgranules according to one of claims 1 and 2, characterized in that they comprise :
- a neutral core coated with a layer containing Ginkgo Biloba extract -with at least one pharmaceutically acceptable excipient,
 - an optional water-repellent layer, coating said core,
- comprising at least a polymer or a thermoplastic excipient,

- an outer polymeric layer which sustain the release of said extract from the active core.

4. Sustained release microgranules according to anyone
5 of claims 1 to 3, characterized in that the neutral core consists of a substance chosen from sugar, starch, mannitol, sorbitol, xylitol, cellulose, talc and mixtures thereof.
- 10 5. Sustained release microgranules according to claim 4, characterized in that the neutral core consists of a starch/sucrose core in 80/20 mass ratios.
- 15 6. Sustained release microgranules according to anyone of claims 1 to 5, characterized in that the Gingko Biloba extract contains up to 40 % by weight of flavonoids, and up to 10 % by weight of terpenes.
- 20 7. Sustained release microgranules according to claim 6, characterized in that the Gingko Biloba extract preferably contains up to 24 % by weight of flavonoids, and up to 6% by weight of terpenes.
- 25 8. Sustained release microgranules according to anyone of claims 3 to 7, characterized in that the layer containing the Gingko Biloba extract contains at least one pharmaceutically acceptable excipient, selected from the group comprising a binder, an antistatic agent or a lubricant, preferably a binder.

9. Sustained release microgranules according to claim 8, characterized in that the binder is selected from the group consisting of cellulosic polymers, such as ethylcellulose, hydroxypropylcellulose and
5 hydroxypropylmethyl cellulose, acrylic polymers, such as insoluble acrylate ammoniomethacrylate copolymer, polyacrylate as polymethacrylic copolymer, povidones, copovidones, polyvinylalcohols, shellac, alginic acid, sodium alginate, starch, pregelatinized starch, sucrose
10 and its derivatives, guar gum, polyethylene glycol, preferably polyvinylpyrrolidone (PVP) or shellac.

10. Sustained release microgranules according to claim 9, characterized in that the binder is used in
15 proportions of at most about 50 %, preferably at most 20 % by weight of Gingko Biloba extract.

11. Sustained release microgranules according to anyone of claims 8 to 10, characterized in that the antistatic
20 agent, which can be used as flow aid, is selected from the group consisting of micronised or non micronised talc, fumed silica, colloidal silica, precipitated silica and mixtures thereof.

25 12. Sustained release microgranules according to claim 11, characterized in that the antistatic agent is used in proportions of at most 5%, preferably 2% by weight relative to the weight of said granules of Gingko Biloba.

13. Sustained release microgranules according to anyone of claims 8 to 12, characterized in that the lubricant is selected from the group consisting of magnesium stearate, stearic acid, sodium stearyl fumarate,
5 micronised polyoxyethyleneglycol, leukine, sodium benzoate and mixtures thereof.

14. Sustained release microgranules according to claim 13, characterized in that the amount of lubricant is
10 from 0 to 3%, preferably from 1 to 2% by weight, based on the weight of the granules.

15. Sustained release microgranules according to anyone of claims 3 to 14, characterized in that the
15 intermediate water-repellent layer comprises at least a polymer or a thermoplastic excipient.

16. Sustained release microgranules according to claim 15, characterized in that the polymer is selected from
20 the group consisting of cellulosic polymers, such as ethylcellulose, hydroxypropylcellulose and hydroxypropylmethyl cellulose, acrylic polymers, such as insoluble acrylate ammoniomethacrylate copolymer, polyacrylate as polymethacrylic copolymer, povidones,
25 copovidones, polyvinylalcohols, shellac, alginic acid, sodium alginate, starch, pregelatinized starch, sucrose and its derivatives, guar gum, polyethylene glycol, preferably polyvinylpyrrolidone (PVP) or shellac.

17. Sustained release microgranules according to anyone of claims 3 to 16, characterized in that the outer polymeric layer contains at least one coating agent selected from the group consisting of cellulosic
5 polymers, acrylic polymers, shellac and mixtures thereof.

18. Sustained release microgranules according to claim 17, characterized in that the cellulosic polymer is
10 selected among ethylcellulose, hydroxypropylcellulose and/or hydroxypropylmethylcellulose.

19. Sustained release microgranules according to claim 17, characterized in that the acrylic polymer is
15 selected from insoluble acrylate ammonio-methacrylate copolymer, polyacrylate, or methacrylic copolymers, and combinations thereof.

20. Sustained release microgranules according to claim 20 19, characterized in that the outer polymeric layer additionally contains a plasticizer, a surfactant, an antistatic agent and/or a lubricant.

21. Sustained release microgranules according to claim 20, characterized in that the plasticizer is selected
25 in the group consisting of dibutyl sebacate, triacetine, triethylacetate, triethylcitrate, ethylphthalate, or mixtures thereof.

22. Sustained release microgranules according to claim 21, characterized in that the plasticizer is used in proportions of at most about 30 %, preferably 10 % by weight of the coating polymers.

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23. Sustained release microgranules according to anyone of claims 8 to 22, characterized in that the antistatic agent is selected from the group comprising micronised or non micronised talc, fumed silica, colloidal silica, precipitated silica and mixtures thereof.

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24. Sustained release microgranules according to claim 23, characterized in that the antistatic agent is used in proportions of at most about 10 %, preferably between 0 and 3% by weight, more preferably less than 1% by weight.

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25. Process for the preparation of sustained release microgranules according to anyone of claims 1 to 24, characterized in that it comprises the successive steps consisting of :

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- applying over a neutral core, a layer comprising Ginkgo Biloba extract, and at least one pharmaceutical excipient, preferably a binder.
- 25 - coating said core with an intermediate layer over the thus obtained granules by spraying thereon a suspension, or a solution comprising a polymer or a thermoplastic excipient

- coating the thus coated granules with an outer layer by spraying a suspension, a dispersion or a solution of a sustained-release coating composition,
- drying the thus obtained coated granules.

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26. Process for the preparation of sustained release microgranules according to claim 25, characterized in that the layer is applied over the neutral cores by spraying a coating alcoholic or aqueous alcoholic solution containing the Gingko Biloba extracts and the excipient.

27. Process for the preparation of sustained release microgranules according to claim 26, characterized in that the alcoholic or aqueous alcoholic solution contains isopropyl alcohol.

28. Process for the preparation of sustained release microgranules according to claim 26, characterized in that the layer applied over the neutral cores is a 10 % w/w binding solution of shellac dissolved in isopropyl alcohol.

29. Process for the preparation of sustained release microgranules according to anyone of claims 25 to 28, characterized in that the outer coating layer is a water dispersion of ethylcellulose at 16 % w/w containing 25 % w/w of dibutyl sebacate versus dry polymer.